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CHARACTERISTICS OF THE HALOGENATION OF 2-SUBSTITUTED 6-BENZHYDRYL-4(3H)-PYRIMIDINONES

I. A. Novakov, B. S. Orlinson, and M. B. Nawrozkij

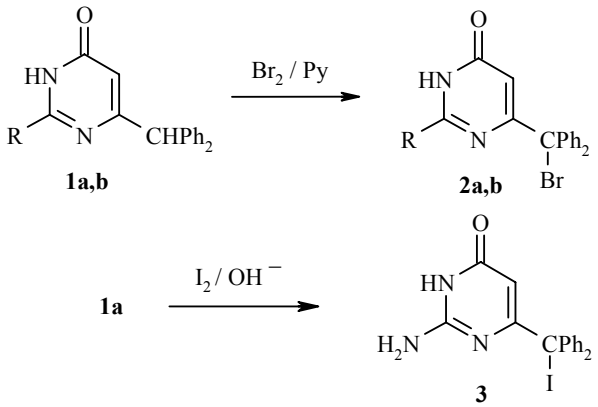
The halogenation of 2-substituted 6-benzhydryl-4(3H)-pyrimidinones has been investigated. Bromination with Py·Br_2 and iodination with I_2 solution in alkali occurs exclusively at the CH hydrogen of the benzhydryl group.

Keywords: 6-benzhydryl-4(3H)-pyrimidinones, bromination, halogenation, iodination.

Derivatives of 6-benzhydryl-4(3H)-pyrimidinones with alkoxy [1], alkylamino [2], or alkylsulphanyl [3] groups in position 2 of the pyrimidine heterocycle are of considerable interest as antiviral materials. At the same time their analogs containing benzhydryl units in position 6 of the pyrimidine ring, are devoid of anti-HIV1 activity, but possess cytotoxic properties [4].

In a continuation of the study of new derivatives of 6-benzhydryl-4(3H)-pyrimidinones as possible cytotoxic agents, we have investigated the halogenation of 2-amino-6-benzhydryl-4(3H)-pyrimidinone (**1a**) and 6-benzhydryl-2-(methylsulfanyl)-4(3H)-pyrimidinone (**1b**). As a result it has been shown that both bromination and iodination of compound **1a** occurs at the CH group of the benzhydryl fragment, even in the absence of a free radicals initiator, to give 2-amino-6-[bromo(diphenyl)methyl]-4(3H)-pyrimidinone (**2a**) and 2-amino-6-[iodo(diphenyl)methyl]-4(3H)-pyrimidinone (**3**) respectively.

Scheme 1



1, 2 a R = NH_2; **b** R = SMe

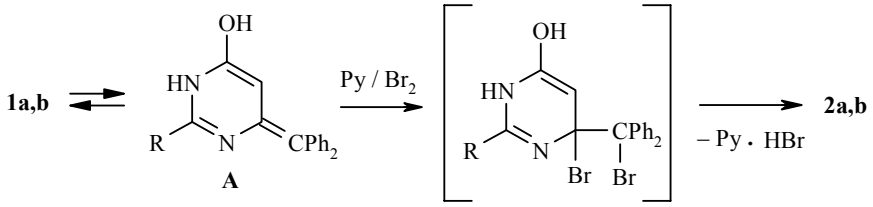
Volgograd State Technical University, Volgograd 400131, Russia; e-mail: thiouracil@rambler.ru. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, 1418-1420, September, 2006. Original article submitted May 19, 2005.

In further study we have shown that bromination of compound **1b** also occurs at the CH group of the benzhydryl fragment to give 6-[bromo(diphenyl)methyl]-2-(methylsulfanyl)-4(3H)-pyrimidinone (**2b**).

The signal of the CH proton of the benzhydryl group (in the region of 5.3 ppm) is absent from the ^{1}H NMR spectrum of compounds **2a,b** and **3** but the signal of the C(5)H proton of the pyrimidine ring (in the 5.9-6.0 ppm region) is retained.

It should be noted that the direction of the halogenation is not trivial. It has been shown previously [5] that both bromination and iodination of 6-alkyl- and 6-(arylmethyl)-4(3H)-pyrimidinones occurs exclusively at position 5 of the heterocycle. Since addition, not substitution, is characteristic of pyridine dibromide [6], it is possible that the change in direction of bromination of compounds **1a,b** is connected with the participation of the tautomeric form **A** (Scheme 2), stabilized by two phenyl groups.

Scheme 2



In the case of the iodination reaction, the halogenating reagent is the $I^- - IO^-$ system (the product of the reaction of I_2 with aqueous alkali) which also indicates that the reaction may proceed by an addition-elimination mechanism.

Compounds **1a,b** were synthesized according to a method described previously [7], by the reaction of methyl (4,4-diphenyl-3-oxo)butanoate (**4**) with guanidine or 5-methylisothiourea respectively.

EXPERIMENTAL

^{1}H NMR spectra of DMSO-d_6 solution with HMDS as internal standard (δ = 0.05 ppm) were recorded on a Varian-Mercury 300B (301 MHz). Melting points were determined with MelTemp 3.0 instrument at rate of heating of 10°C/min.

Methyl 4,4-Diphenyl-3-oxobutanoate (4) was prepared by a method we have described [8]. Yield 98%; bp 172-174° (1-2 mm Hg), n^{20}_D 1.5654 which agree with the literature results [9].

6-Diphenylmethyl-2-(methylsulfanyl)-4(3H)-pyrimidinone (1b). A mixture of 50% aqueous solution of K_2CO_3 (5.2 g, 37.6 mmol), the ester **4** (5 g, 18.6 mmol), EtOH (15 ml), and $(H_2NC(SMe)NH)_2 \cdot H_2SO_4$ (5.2 g, 18.7 mmol) was stirred at room temperature for 1 week, neutralized with 1N HCl, the reaction product was filtered off, dried, and crystallized. Yield 4.0 g (70%); mp 234-236°C (DMF–EtOH) which agrees with literature data [9].

2-Amino-6-diphenylmethyl-4(3H)-pyrimidinone Sesquihydrate (1a·1.5H$_2$O). A solution of ester **4** (5 g, 18.6 mmol), $(H_2N)_2CNH \cdot AcOH$ (4.5 g, 37.8 mmol), and NaOMe (3 g, 55.5 mmol) in abs. MeOH (100 ml) was boiled for 72 h with the exclusion of moisture and CO_2. The solvent was removed in vacuum, 1N AcOH (100 ml) was added to the residue, the desired product was filtered off, dried and crystallized. Yield 3.8 g (67%); mp 167°C (- H_2O), 237°C anhydrous (EtOH). ^{1}H NMR spectrum, δ, ppm (J, Hz): 5.07 (1H, d, J = 6.11, 5-CH); 5.17 (1H, d, J = 4.89, CH); 6.51 (2H, s, NH_2); 7.14-7.27 (10H, m, $(C_6H_5)_2$); 10.70 (1H, s, NH). Found, %: C 66.50; H 6.01; N 13.73. $C_{17}H_{15}N_3O \cdot 1.5H_2O$. Calculated, %: C 67.09; H 5.96; N 13.81.

6-[Bromo(diphenyl)methyl]-2-(methylsulfanyl)-4(3H)-pyrimidinone (2b). Bromine (0.35 ml, 1.09 g, 6.8 mmol) was added to a suspension of pyrimidinone **1b** (2 g, 6.8 mmol) in a mixture of anhydrous Py (6 ml, 5.87 g, 74.3 mmol) and anhydrous DMF (10 ml). The reaction mixture was stirred for 5 h at room temperature, diluted with water (150 ml) and extracted with $CHCl_3$ (4 × 50 ml). The organic phase was consolidated, washed with water (2 × 50 ml), saturated $Na_2S_2O_5$ (25 ml), the brine (2 × 25 ml), and dried over Na_2SO_4. It was filtered, the filtrate was concentrated in vacuum and the residue was concentrated in vacuum with toluene (25 ml) and crystallized. Yield 1.9 g (76%); mp 228-230°C (PhMe). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.23 (3H, s, CH_3); 5.76 (1H, s, 5-CH); 7.18-7.26 (10H, s, $(C_6H_5)_2$); 13.21 (1H, br. s, NH). Found, %: C 55.42; H 3.94; Br 20.60; N 7.03; S 8.07. $C_{18}H_{15}BrN_2OS$. Calculated, %: C 55.82; H 3.90; Br 20.63; N 7.23; S 8.28.

2-Amino-6-[bromo(diphenyl)methyl]-4(3H)-pyrimidinone (2a) was prepared analogously to compound **2b**. Yield 61%; mp 287-288°C (dec.) (EtOH). ^{1}H NMR spectrum, δ, ppm: 5.76 (1H, s, 5-CH); 6.65 (2H, s, NH_2); 7.16-7.23 (10H, m, $(C_6H_5)_2$); 11.31 (1H, s, NH). Found, %: C 56.99; H 3.90; Br 22.51; N 11.47. $C_{17}H_{14}BrN_3O$. Calculated, %: C 57.23; H 3.96; Br 22.43; N 11.80.

2-Amino-6-[iodo(diphenyl)methyl]-4(3H)-pyrimidinone (4). Pyrimidinone sesquihydrate **1a**·$1.5H_2O$ (1.5 g, 4.9 mmol) was added to solution of KOH (0.4 g, 6.0 mmol) in water (20 ml) and the mixture was heated to form a clear solution. The solution was cooled to room temperature, CH_2Cl_2 (40 ml) and iodine (1.4 g, 5.5 mmol) were added and the reaction mixture was stirred vigorously at room temperature for 5 h, saturated aqueous solution of $Na_2S_2O_5$ (10 ml) was added and the mixture was stirred for 5 min more. The precipitate was filtered off and crystallized. Yield 0.7 g (35%); mp 273-274°C (dec.) (EtOH–DMF). ^{1}H NMR spectrum, δ, ppm: 5.76 (1H, s, 5-CH); 6.60 (2H, s, NH_2); 7.16-7.23 (10H, m, $(C_6H_5)_2$); 11.14 (1H, s, NH). Found, %: C 50.50; H 3.50; I 30.99; N 10.33. $C_{17}H_{14}IN_3O$. Calculated, %: C 50.64; H 3.50; I 31.74; N 10.42.

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